

Dr. Greene contrasted this with the customary method for inhibiting binding to a functionally critical site by placing an inhibitor directly at the functionally critical site thereby permitting the inhibitor to physically impede binding of an activating compound to the receptor site (i.e., competitive inhibition). Dr. Greene pointed out that this was entirely different from the present invention, which does not inhibit the function of the critical site by interposing a physical barrier, but rather, alters the geometry of the critical site due to allosteric modification of the protein structure. Thus, in the present invention, interaction at a functionally critical site is disrupted by the binding of a distinct compound at a distant site (the allosteric cavity).

Dr. Greene pointed out that the functionally critical site on the target protein could be determined using a 3D model of the protein, and that such a model could be prepared using various techniques including e.g., crystallography, NMR, homology modeling and computer simulation using standard software such as Insight II and Quanta (reference specification page 11 lines 30-31). Once the 3D model of the protein is available, the allosteric cavity (to which the modulating compound is targeted) is identified using e.g., off-the-shelf software such as MS, or Insight II (commercially available from Accelrys Inc.). Once an allosteric cavity is identified, dimensions of the cavity and its chemical and/or electrostatic properties are mapped (using the same software e.g., Insight II or MS). Using the information obtained by mapping, compounds containing functional groups that could be accommodated by the cavity (i.e., bind in the cavity) are identified and such compounds are tested in an *in vitro* assay to determine if they cause an allosteric modification of the intermolecular interaction at the functionally critical site (on the target protein).

Dr. Greene explained that the technology used to prepare a 3-dimensional (3D) model of a protein (e.g., the protein on which the functionally critical site is located) and to map the protein's surface and the cavity was well known at the time the invention was made and widely used in commercial and research laboratories.

Dr. Greene distinguished the present invention from the Li reference, pointing out that Li teaches a method for identifying compounds that bind to a functionally critical site (an epitope) on

Examiner Marschel also suggested describing the cavity as employed in practicing the invention as an allosteric cavity. This suggestion has been adopted in the amended claim 1, and in new claims 26-29 (which are variations of claim 1 for the Examiner's consideration).

Support for the new claims can be found in the specification (published PCT WO 00/01349) at page 8, lines 20-23, which states that the functionally critical site refers to a region or location or secondary structural element on a target protein that is involved in either altering or mediating function, *the modulation of which is desirable* (emphasis supplied). Thus, it is presumed that before one can allosterically modulate function, the function to be modulated must be predetermined (i.e., known and of interest to the skilled artisan to modulate). Further support for the new claims is found at page 10, lines 6-10, which states that "Since the interaction with modifiers is necessary for a specific biological function attributed to the target protein, inhibition of the target protein:modifier interaction inhibits the *biological function associated with such interaction*" (emphasis supplied).

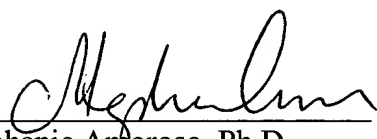
At the conclusion of the interview, Examiner Ly indicated that he would withdraw the enablement rejection and would likely withdraw the prior art rejection based on the Li reference after further consideration.

Based on the Examiner's suggestions at the interview, claim 1 has been amended to further clarify the method of the invention and the manner in which it is practiced. New claims have been added as alternatives to claim 1. The amended and new claims are fully supported in the specification and are believed to be in condition for allowance. Should the Examiner find claims 26-30 allowable in lieu of claim 1 the pending claims depending from claim 1 will be amended to depend from the allowable claim.

This application is now believed to be in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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